10/513699

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  NEWS 2 DEC 01 ChemPort single article sales feature unavailable
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  NEWS 4 APR 07 STN is raising the limits on saved answers
  NEWS 5 APR 24 CA/CAplus now has more comprehensive patent assignee
                  information
  NEWS 6 APR 26 USPATFULL and USPAT2 enhanced with patent
                  assignment/reassignment information
  NEWS 7 APR 28 CAS patent authority coverage expanded
  NEWS 8 APR 28 ENCOMPLIT/ENCOMPLIT2 search fields enhanced
  NEWS 9 APR 28 Limits doubled for structure searching in CAS
                  REGISTRY
  NEWS 10 MAY 08 STN Express, Version 8.4, now available
  NEWS 11 MAY 11 STN on the Web enhanced
  NEWS 12 MAY 11 BEILSTEIN substance information now available on
                  STN Easy
  NEWS 13 MAY 14 DGENE, PCTGEN and USGENE enhanced with increased
                  limits for exact sequence match searches and
                  introduction of free HIT display format
  NEWS 14 MAY 15 INPADOCDB and INPAFAMDB enhanced with Chinese legal
                  status data
  NEWS 15 MAY 28 CAS databases on STN enhanced with NANO super role in
                  records back to 1992
  NEWS 16 JUN 01 CAS REGISTRY Source of Registration (SR) searching
                  enhanced on STN
  NEWS 17 JUN 26 NUTRACEUT and PHARMAML no longer updated

  NEWS 18 JUN 29 IMSCOPROFILE now reloaded monthly

  NEWS 19 JUN 29 EPFULL adds SLART to AB, MCLM, and TI fields

  NEWS EXPRESS MAY 26 09 CURRENT WINDOWS VERSION IS V8.4,
               AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2009.

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<12/04/2007>   Erich Leese

* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 15:34:53 ON 30 JUN 2009

=> file reg
COST IN U.S. DOLLARS   SINCE FILE   TOTAL
                                                     ENTRY   SESSION
FULL ESTIMATED COST   0.22   0.22

FILE 'REGISTRY' ENTERED AT 15:35:04 ON 30 JUN 2009
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STRUCTURE FILE UPDATES: 29 JUN 2009 HIGHEST RN 1160357-19-6
DICTIONARY FILE UPDATES: 29 JUN 2009 HIGHEST RN 1160357-19-6

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=>
Uploading C:\Program Files\Stnexp\Queries\10594105carbonyl.str
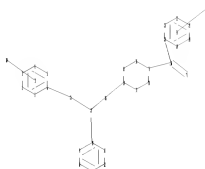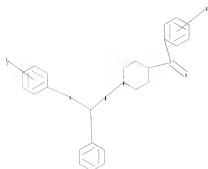
chain nodes :
25 26 27 30 34 36 37
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
24
chain bonds :
6-25 10-27 14-26 17-36 20-36 25-27 26-27 36-37
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12 13-14 13-18
14-15 15-16 16-17 17-18 19-20 19-24 20-21 21-22 22-23 23-24
exact/norm bonds :
6-25 13-14 13-18 14-15 14-26 15-16 16-17 17-18 25-27 26-27 36-37
exact bonds :
10-27 17-36 20-36
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12 19-20 19-24
20-21 21-22 22-23 23-24
isolated ring systems :
containing 1 : 7 : 13 : 19 :

G1:C,N

G2:CF2,CF3,CCl2,CCl3,CBr2,CBr3,X

G3:C,N

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:CLASS 26:CLASS 27:CLASS 30:CLASS
 31:Atom 34:CLASS 35:Atom 36:CLASS 37:CLASS

10/513699

L1   STRUCTURE UPLOADED

=> s l1 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 185.40 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 15:35:29 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   685 TO ITERATE

100.0% PROCESSED   685 ITERATIONS   6 ANSWERS
SEARCH TIME: 00.00.01

L2   6 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS   SINCE FILE   TOTAL
                                                  ENTRY   SESSION
FULL ESTIMATED COST   185.88   186.10

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FILE COVERS 1907 - 30 Jun 2009 VOL 151 ISS 1
FILE LAST UPDATED: 29 Jun 2009 (20090629/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Apr 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Apr 2009

CAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2009.

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s l2 full
L3   2 L2

=> d ibib abs hitstr tot

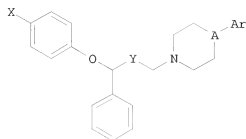<12/04/2007>   Erich Leese

10/513699

THE ESTIMATED COST FOR THIS REQUEST IS 11.28 U.S. DOLLARS
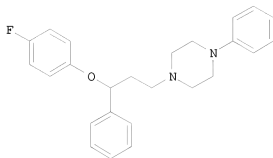DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:y

<12/04/2007>   Erich Leese

```
L3   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:      2005:1103625  CAPLUS
DOCUMENT NUMBER:       143:387060
TITLE:                 Preparation of piperazine or piperidine derivatives as
                       serotonin reuptake inhibitors
INVENTOR(S):           Pinney, Kevin G.; Miranda, Maria Graciela; Dorsey,
                       James Michael
PATENT ASSIGNEE(S):    Baylor University, USA
SOURCE:                PCT Int. Appl., 52 pp.
                       CODEN: PIXXD2
DOCUMENT TYPE:         Patent
LANGUAGE:              English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

      PATENT NO.          KIND   DATE       APPLICATION NO.         DATE
      ---------------     ----   --------   --------------------    --------
      WO 2005094896       A2     20051013   WO 2005-US10356         20050328
      WO 2005094896       A3     20070503
          W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
              CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
              GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
              LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
              NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM,
              SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
          RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
              AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
              EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
              RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
              MR, NE, SN, TD, TG, AP, EA, EP, OA
      EP 1732610          A2     20061220   EP 2005-730778          20050328
          R:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
              IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA,
              HR, LV, MK, YU
      US 20080132514      A1     20080605   US 2007-594105          20070921
PRIORITY APPLN. INFO.:                      US 2004-557069P    P   20040326
                                            WO 2005-US10356    W   20050328
OTHER SOURCE(S):       CASREACT 143:387060; MARPAT 143:387060
GI
```

I

II

AB   Title compds. I [X = F or CF3; Y = (CH2)n; n = 0-1; A = N or C; Ar = aryl]
      and their pharmaceutically acceptable salts, are prepared and disclosed as
      serotonin reuptake inhibitors. Thus, e.g., II was prepared by reduction of
      1-phenyl-3-(4-phenyl-piperazin-1-yl)-propan-1-ol (preparation given) using
      sodium borohydride followed by coupling with 4-fluorophenol. The ability
      of I to inhibit [3H]5-HT uptake was evaluated using liquid scintillation
      spectroscopy and it was revealed that selected compds. of the invention
      possessed IC50 values in the range of 1.45 up to 9.56 μM. I as
      serotonin reuptake inhibitors should prove useful in the treatment of
      depression. Pharmaceutical composition comprising I are disclosed.
IT   866548-42-7P 866548-43-8P 866548-44-9P
      866548-45-0P
      RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
      (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
      (Uses)
          (preparation of piperazine or piperidine derivs. as serotonin reuptake
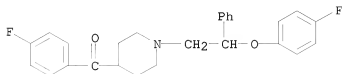   inhibitors)
RN   866548-42-7 CAPLUS
CN   Methanone, [1-[2-(4-fluorophenoxy)-2-phenylethyl]-4-piperidinyl](4-
      fluorophenyl)- (CA INDEX NAME)
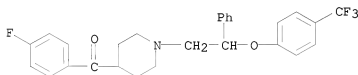

RN   866548-43-8 CAPLUS

CN   Methanone, [1-[2-(4-fluorophenoxy)-2-phenylethyl]-4-piperidinyl](4-
     fluorophenyl)-, hydrochloride (1:1) (CA INDEX NAME)
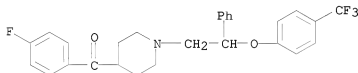

● HCl

RN   866548-44-9 CAPLUS
CN   Methanone, (4-fluorophenyl)[1-[2-phenyl-2-[4-
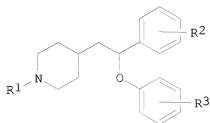   (trifluoromethyl)phenoxy]ethyl]-4-piperidinyl]- (CA INDEX NAME)

RN   866548-45-0 CAPLUS
CN   Methanone, (4-fluorophenyl)[1-[2-phenyl-2-[4-
     (trifluoromethyl)phenoxy]ethyl]-4-piperidinyl]-, hydrochloride (1:1) (CA
     INDEX NAME)

● HCl

<12/04/2007>   Erich Leese

I

AB   In a wide search program toward new, efficient, and fast-acting
     antidepressant drugs, series of new compds. having an
     (aryl)(aryloxy)methyl moiety linked directly or through a methylene chain
     to different substituted and unsubstituted cycles (isoquinoline,
     piperazine, piperidine, tetrahydropyran, or cyclopentane) were prepared
     These compds. have been evaluated for their affinities for serotonin
     (5-HT) transporter (SERT) and 5-HT1A and 5-HT2A receptors. Racemic mixts.
     of 4-[(aryl)(aryloxy)methyl]piperidines I (R1 = H, Me, MeCO; R2 = H, 3-F,
     4-F, 4-Cl, 4-Me; R3 = H, 2-CN, 4-O2N, 4-MeO, 2-Ph, etc.) showed much
     higher affinity values for SERT than fluoxetine and resulted in lack of
     affinity for 5-HT1A and 5-HT2A receptors. Some of these racemic mixts.
     were resolved to their enantiomers and tested for binding to
     norepinephrine (NE) transporter (NET), dopamine (DA) transporter (DAT),
     and α2 receptor. Several of these enantiomers, (-)-I (R1 = R2 = H;
     R3 = 2-F), (-)-I (R1 = R2 = H; R3 = 3-F), (-)-I (R1 = H; R2 = 3-F; R3 =
     2-F), (+)-I (R1 = H; R2 = R3 = 3-F), displayed a dual binding profile with
     affinities for SERT and NET with Ki < 25 nM and a NET/SERT ratio <10.
     (-)-I (R1 = R2 = H; R3 = 3-F) (coded as F-98214-TA for development
     studies) showed a dual binding profile with very high affinity values for
     SERT and NET (Ki = 1.9 and 13.5 nM, resp.), and further pharmacol.
   characterization is in progress for its evaluation as a antidepressant.
IT   639467-63-3P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL
(Biological study); PREP (Preparation)
   (preparation of [(aryl)(aryloxy)alkyl]piperidines and analogs as potential
   antidepressants with high affinity for serotonin and norepinephrine
   transporters)
RN 639467-63-3 CAPLUS
CN Methanone, [1-[3-(2-fluorophenoxy)-3-phenylpropyl]-4-piperidinyl](4-
    fluorophenyl)-, hydrochloride (1:1) (CA INDEX NAME)
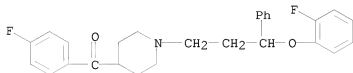
● HCl

REFERENCE COUNT: 40   THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS
                              RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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10/513699


=> d his

     (FILE 'HOME' ENTERED AT 15:34:53 ON 30 JUN 2009)

     FILE 'REGISTRY' ENTERED AT 15:35:04 ON 30 JUN 2009
L1            STRUCTURE UPLOADED
L2           6 S L1 FULL

     FILE 'CAPLUS' ENTERED AT 15:35:33 ON 30 JUN 2009
L3           2 S L2 FULL

=> file reg
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY      SESSION
FULL ESTIMATED COST                               14.78       200.88

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                   ENTRY      SESSION
CA SUBSCRIBER PRICE                               -1.64       -1.64

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DICTIONARY FILE UPDATES:  29 JUN 2009  HIGHEST RN 1160357-19-6

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experimental property data in the original document.  For information
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http://www.cas.org/support/stngen/stndoc/properties.html

=>
Uploading C:\Program Files\Stnexp\Queries\10594105last.str
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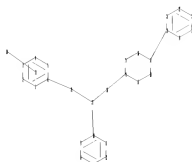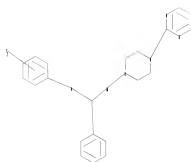
```
chain nodes :
25   26   27   30
ring nodes :
1   2   3   4   5   6   7   8   9   10   11   12   13   14   15   16   17   18   19   20   21   22   23
24
chain bonds :
6-25   10-27   14-26   17-20   25-27   26-27
ring bonds :
1-2   1-6   2-3   3-4   4-5   5-6   7-8   7-12   8-9   9-10   10-11   11-12   13-14   13-18
14-15   15-16   16-17   17-18   19-20   19-24   20-21   21-22   22-23   23-24
exact/norm bonds :
6-25   13-14   13-18   14-15   14-26   15-16   16-17   17-18   17-20   25-27   26-27
exact bonds :
10-27
normalized bonds :
1-2   1-6   2-3   3-4   4-5   5-6   7-8   7-12   8-9   9-10   10-11   11-12   19-20   19-24
20-21   21-22   22-23   23-24
isolated ring systems :
containing 1 : 7 : 13 : 19 :


G1:C,N

G2:CF2,CF3,CCl2,CCl3,CBr2,CBr3,X

G3:C,N

Match level :
1:Atom   2:Atom   3:Atom   4:Atom   5:Atom   6:Atom   7:Atom   8:Atom   9:Atom   10:Atom
11:Atom   12:Atom   13:Atom   14:Atom   15:Atom   16:Atom   17:Atom   18:Atom   19:Atom
20:Atom   21:Atom   22:Atom   23:Atom   24:Atom   25:CLASS   26:CLASS   27:CLASS   30:CLASS
 31:Atom
```

```
L4      STRUCTURE UPLOADED

=> d l4
L4 HAS NO ANSWERS
L4             STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.


=> s l4 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 185.40 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 15:39:54 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     283 TO ITERATE

100.0% PROCESSED     283 ITERATIONS                          6 ANSWERS
SEARCH TIME: 00.00.01

L5           6 SEA SSS FUL L4

=> file caplus
COST IN U.S. DOLLARS                         SINCE FILE      TOTAL
                                                 ENTRY      SESSION
FULL ESTIMATED COST                             185.88       386.76

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)   SINCE FILE      TOTAL
                                                 ENTRY      SESSION
CA SUBSCRIBER PRICE                               0.00        -1.64

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FILE LAST UPDATED: 29 Jun 2009  (20090629/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Apr 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Apr 2009

CAplus now includes complete International Patent Classification (IPC)
```

reclassification data for the second quarter of 2009.

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

```
=> s l5 full
L6          7 L5

=> d ibib abs hitstr tot
THE ESTIMATED COST FOR THIS REQUEST IS 39.48 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:y
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L6   ANSWER 1 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2009:412461 CAPLUS
DOCUMENT NUMBER: 151:496
TITLE: QSAR study of the 5-HT1A receptor affinities of
                        arylpiperazines using a genetic algorithm-artificial
                        neural network model
AUTHOR(S):   Habibi-Yangjeh, Aziz
CORPORATE SOURCE: Department of Chemistry, Faculty of Science,
                        University of Mohaghegh Ardabili, Ardabil, Iran
SOURCE: Monatshefte fuer Chemie (2009), 140(5), 523-530
                        CODEN: MOCMB7; ISSN: 0026-9247
PUBLISHER: SpringerWienNewYork
DOCUMENT TYPE: Journal
LANGUAGE: English

AB   Genetic algorithm-multiparameter linear regression (GA-MLR) and genetic
      algorithm-artificial neural network (GA-ANN) models have been used for
      prediction of the 5-HT1A receptor affinities (pK i) of 66 arylpiperazines.
      A large number of theor. descriptors were calculated for each compound The
genetic
      algorithm (GA) was used for selection of the variables that resulted in
      the best fit to the MLR and ANN models. The models were generated using
      seven descriptors as variables. For evaluation of the predictive power of
      the models, pK i values of 13 compds. in the prediction set were calculated
      Mean percentage deviation (MPD) for the GA-MLR and GA-ANN models were
      0.344 and 0.065, resp. Comparison of the results obtained by use of the
      models reveals the GA-ANN model is superior to the GA-MLR model.
      Graphical abstract
IT   328248-23-3
      RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic
      use); BIOL (Biological study); USES (Uses)
         (QSAR study of 5-HT1A receptor affinities of arylpiperazines using a
      genetic algorithm-artificial neural network model)
RN   328248-23-3 CAPLUS
CN   Pyrimidine, 2-[4-[3-phenyl-3-[4-(trifluoromethyl)phenoxy]propyl]-1-
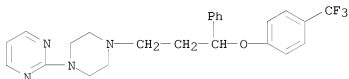   piperazinyl]- (CA INDEX NAME)
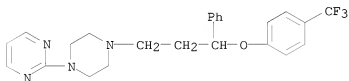
REFERENCE COUNT: 46   THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS
                              RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L6    ANSWER 2 OF 7  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:        2008:803320  CAPLUS
DOCUMENT NUMBER:         149:215113
TITLE:                   Two-dimensional QSAR studies on arylpiperazines as
                         high-affinity 5-HT1A receptor ligands
AUTHOR(S):               Weber, Karen C.; Honorio, Kathia M.; Andricopulo,
                         Adriano D.; Da Silva, Alberico B. F.
CORPORATE SOURCE:        Instituto de Quimica de Sao Carlos, Universidade de
                         Sao Paulo, Sao Carlos, 13560-970, Brazil
SOURCE:                  Medicinal Chemistry (2008), 4(4), 328-335
                         CODEN: MCEHAJ; ISSN: 1573-4064
PUBLISHER:               Bentham Science Publishers Ltd.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
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AB   5-HT1A receptor plays an important role in the delayed onset of
      antidepressant action of a class of selective serotonin reuptake
      inhibitors. Moreover, 5-HT1A receptor levels have been shown to be
      altered in patients suffering from major depression. In this work,
      hologram quant. structure-activity relationship (HQSAR) studies were
      performed on a series of arylpiperazine compds. presenting affinity to the
      5-HT1A receptor. The models were constructed with a training set of 70
      compds. The most significant HQSAR model (q2 = 0.81, r2 = 0.96) was
      generated using atoms, bonds, connections, chirality, and donor and
      acceptor as fragment distinction, with fragment size of 6-9. Predictions
      for an external test set containing 20 compds. are in good agreement with
      exptl. results showing the robustness of the model. Addnl., useful
      information can be obtained from the 2D contribution maps.

```
IT    328248-23-3
      RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
      (Biological study); USES (Uses)
         (two-dimensional QSAR studies on arylpiperazines as high-affinity
         5-HT1A receptor ligands)
RN    328248-23-3  CAPLUS
CN    Pyrimidine, 2-[4-[3-phenyl-3-[4-(trifluoromethyl)phenoxy]propyl]-1-
      piperazinyl]-  (CA INDEX NAME)
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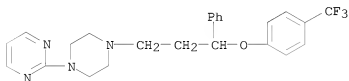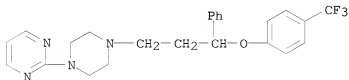


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REFERENCE COUNT:         31    THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L6   ANSWER 3 OF 7  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:      2008:767635  CAPLUS
DOCUMENT NUMBER:       149:324283
TITLE:                 Quantitative structure-affinity relationship of 5-HT1A
                       receptor ligands by the classification tree method
AUTHOR(S):             Kuz'min, V. E.; Polischuk, P. G.; Artemenko, A. G.;
                       Makan, S. Yu.; Andronati, S. A.
CORPORATE SOURCE:      A.V. Bogatsky Physical-Chemical Institute, National
                       Academy of Sciences of Ukraine, Odessa, Ukraine
SOURCE:                SAR and QSAR in Environmental Research (2008),
                       19(3-4), 213-244
                       CODEN: SQERED; ISSN: 1062-936X
PUBLISHER:             Taylor & Francis Ltd.
DOCUMENT TYPE:         Journal
LANGUAGE:              English
AB   The influence of mol. structure of 346 ligands on their affinity for
     5-HT1A receptors was investigated.  It was shown that the effectiveness of
     the proposed novel approach for interpretation of decision tree models
     compared favorably with the PLS method.  In the context of the proposed
     approach, mol. fragments and their values of the relative influence on the
     affinity for 5-HT1A receptors were defined.
IT   328248-23-3
     RL: ANT (Analyte); BSU (Biological study, unclassified); PRP (Properties);
     ANST (Analytical study); BIOL (Biological study)
        (quant. structure-affinity relationship of 5-HT1A receptor ligands by
        the classification tree method)
RN   328248-23-3  CAPLUS
CN   Pyrimidine, 2-[4-[3-phenyl-3-[4-(trifluoromethyl)phenoxy]propyl]-1-
     piperazinyl]-  (CA INDEX NAME)
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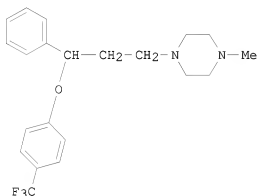


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L6   ANSWER 4 OF 7 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:232006 CAPLUS
DOCUMENT NUMBER: 148:440268
TITLE: A chemometric study of the 5-HT1A receptor affinities
                        presented by arylpiperazine compounds
AUTHOR(S):   Weber, Karen C.; da Silva, Alberico B. F.
CORPORATE SOURCE: Instituto de Quimica de Sao Carlos, Universidade de
                        Sao Paulo, Sao Carlos, 13566-590, Brazil
SOURCE: European Journal of Medicinal Chemistry (2008), 43(2),
                        364-372
                        CODEN: EJMCA5; ISSN: 0223-5234
PUBLISHER: Elsevier Masson SAS
DOCUMENT TYPE: Journal
LANGUAGE: English
AB   Arylpiperazine compds. are promising 5-HT1A receptor ligands that can
     contribute for accelerating the onset of therapeutic effect of selective
     serotonin reuptake inhibitors. In the present work, the chemometric
     methods HCA, PCA, KNN, SIMCA and PLS were employed in order to obtain SAR
     and QSAR models relating the structures of arylpiperazine compds. to their
     5-HT1A receptor affinities. A training set of 52 compds. was used to
     construct the models and the best ones were obtained with nine topol.
     descriptors. The classification and regression models were externally
     validated by means of predictions for a test set of 14 compds. and have
     presented good quality, as verified by the correctness of classifications,
     in the case of pattern recognition studies, and by the high correlation
     coeffs. (q2 = 0.76, r2 = 0.83) and small prediction errors for the PLS
     regression. Since the results are in good agreement with previous SAR
     studies, we can suggest that these findings can help in the search for
     5-HT1A receptor ligands that are able to improve antidepressant treatment.
IT   328248-23-3
     RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU
     (Therapeutic use); BIOL (Biological study); USES (Uses)
        (chemometric study of 5-HT1A receptor affinities presented by
        arylpiperazine compds. as possible antidepressants)
RN   328248-23-3 CAPLUS
CN   Pyrimidine, 2-[4-[3-phenyl-3-[4-(trifluoromethyl)phenoxy]propyl]-1-
     piperazinyl]- (CA INDEX NAME)

REFERENCE COUNT: 35   THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS
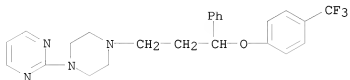   RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

I

AB   Fifteen analogs of benzenepropanamine were synthesized and evaluated for
      their spermicidal as well as microbicidal activities against Trichomonas
      vaginalis and Candida spp. Several compds. showed appreciable dual
      activities. Compound I exhibited good spermicidal (MEC = 0.1%) along with
      substantial anticandidal (MIC = 0.05%) activities, while compds. 3 and 6
      showed significant microbicidal activities with moderate spermicidal
      effect. The SAR of these structures is being discussed here in this
      communication. It is concluded that suitable structural modifications in
      this class of compds. at 3-amino position may lead to a potent spermicide
      with associated microbicidal activity.
IT   911811-11-5P
      RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
      (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
      (Uses)

(benzenepropanamine analogs as non-detergent spermicides with
antitrichomonas and anticandida activities)
RN   911811-11-5 CAPLUS
CN   Pyrimidine, 2-[4-[3-phenyl-3-[4-(trifluoromethyl)phenoxy]propyl]-1-
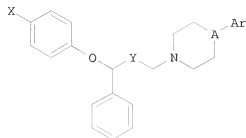piperazinyl]-, hydrochloride (1:2)   (CA INDEX NAME)

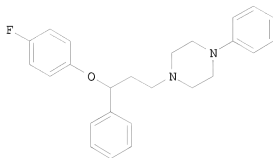

●2 HCl

REFERENCE COUNT: 34   THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS
                                 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L6    ANSWER 6 OF 7  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:       2005:1103625  CAPLUS
DOCUMENT NUMBER:        143:387060
TITLE:                  Preparation of piperazine or piperidine derivatives as
                        serotonin reuptake inhibitors
INVENTOR(S):            Pinney, Kevin G.; Miranda, Maria Graciela; Dorsey,
                        James Michael
PATENT ASSIGNEE(S):     Baylor University, USA
SOURCE:                 PCT Int. Appl., 52 pp.
                        CODEN: PIXXD2
DOCUMENT TYPE:          Patent
LANGUAGE:               English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

      PATENT NO.            KIND    DATE        APPLICATION NO.         DATE
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      WO 2005094896         A2      20051013    WO 2005-US10356         20050328
      WO 2005094896         A3      20070503
          W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
              CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
              GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
              LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
              NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM,
              SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
          RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
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              RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
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      EP 1732610            A2      20061220    EP 2005-730778          20050328
          R:  AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
              IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA,
              HR, LV, MK, YU
      US 20080132514        A1      20080605    US 2007-594105          20070921
PRIORITY APPLN. INFO.:                         US 2004-557069P    P   20040326
                                               WO 2005-US10356    W   20050328
OTHER SOURCE(S):        CASREACT 143:387060; MARPAT 143:387060
GI
```

I

II

AB   Title compds. I [X = F or CF3; Y = (CH2)n; n = 0-1; A = N or C; Ar = aryl] and their pharmaceutically acceptable salts, are prepared and disclosed as serotonin reuptake inhibitors. Thus, e.g., II was prepared by reduction of 1-phenyl-3-(4-phenyl-piperazin-1-yl)-propan-1-ol (preparation given) using sodium borohydride followed by coupling with 4-fluorophenol. The ability of I to inhibit [3H]5-HT uptake was evaluated using liquid scintillation spectroscopy and it was revealed that selected compds. of the invention possessed IC50 values in the range of 1.45 up to 9.56 μM. I as serotonin reuptake inhibitors should prove useful in the treatment of depression. Pharmaceutical composition comprising I are disclosed.

IT   866548-32-5P 866548-33-6P 866548-34-7P
    866548-35-8P
    RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
      (preparation of piperazine or piperidine derivs. as serotonin reuptake inhibitors)

RN   866548-32-5 CAPLUS

CN   Pyrimidine, 2-[4-[2-(4-fluorophenoxy)-2-phenylethyl]-1-piperazinyl]- (CA INDEX NAME)
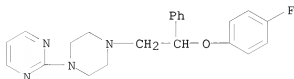
RN   866548-33-6 CAPLUS
CN   Pyrimidine, 2-[4-[2-(4-fluorophenoxy)-2-phenylethyl]-1-piperazinyl]-,
      hydrochloride (1:1) (CA INDEX NAME)
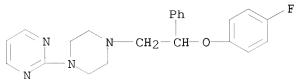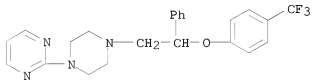

● HCl

RN   866548-34-7 CAPLUS
CN   Pyrimidine, 2-[4-[2-phenyl-2-[4-(trifluoromethyl)phenoxy]ethyl]-1-
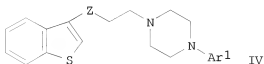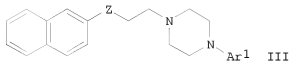   piperazinyl]- (CA INDEX NAME)

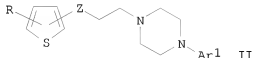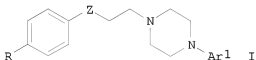RN   866548-35-8 CAPLUS
CN   Pyrimidine, 2-[4-[2-phenyl-2-[4-(trifluoromethyl)phenoxy]ethyl]-1-
      piperazinyl]-, hydrochloride (1:1) (CA INDEX NAME)

● HCl

AB   In a search toward new and efficient antidepressants,
     1-aryl-3-(4-arylpiperazin-1-yl)propane derivs. I (R = H, Ph, MeO, NO2, Z =
     CO, CHOH, CHOR1, R1 = 4-F3CC6H4, 4-MeOC6H4, 3,4-OCH3OC6H3, Ar1 =

2-MeOC6H4, 4-C1C6H4, 2-pyridyl, etc.), II (R = H, 2,5-Me2, 5-Me, 5-NO2, Z
= CO, CNOH, CHOH, CHOR1, R1 = 4-F3CC6H4, 3,4-OCH2OC6H3, 1-C10H7, position
= 2, 3), III and IV (Arl = 2-MeOC6H4, 4-C1C6H4, 2-HOC6H4, Z = CO,CHOH)
were designed, synthesized, and evaluated for 5-HT reuptake inhibition and
5-HT1A receptor antagonism. This dual pharmacol. profile should lead, in
principle, to a rapid and pronounced enhancement in serotoninergic
neurotransmission and consequently to a more efficacious treatment of
depression. The design was based on coupling structural moieties related
to inhibition of serotonin reuptake, such as γ-phenoxypropylamines,
to arylpiperazines, typical 5-HT1A ligands. In binding studies, several
compds. showed affinity at the 5-HT transporter and 5-HT1A receptors.
Antidepressant-like activity was initially assayed in the forced swimming
test with those compds. with Ki < 200 nM in both binding studies.
Functional characterization was performed by measuring the intrinsic
effect on rectal temperature in mice and also the antagonism to
8-OH-DPAT-induced hypothermia. The most efficacious compds. II (R = H, Z
= CHO-1-C10H7, position = 3, Arl = 2-MeOC6H4) (V), II[R = 5-Me, Z =
(E)-CNOH, position = 2, Ar1 = 2-MeOC6H4] and IV (Z = CO, CHOH, Arl =
2-MeOC6H4) (VI) were further explored for their ability to antagonize
8-OH-DPAT-induced inhibition of forskolin-stimulated cAMP formation in a
cell line expressing the 5-HT1A receptor. Furthermore, the
antidepressant-like properties of V and VI, which exhibited 5-HT1A
receptor antagonistic property in the latter study, were also evaluated in
the learned helplessness test in rats. Among these three compds., VI (Z =
CHOH) (1-benzo[b]thiophene-3-yl)-3-[4-(2-methoxyphenyl)-1-ylpropan-1-ol]
showed the higher affinity at both the 5-HT transporter and 5-HT1A
receptors (Ki = 20 nM in both cases) and was also active in the other
pharmacol. tests. Such a pharmacol. profile could lead to a new class of
antidepressants with a dual mechanism of action and a faster onset of
action.

IT   328248-23-3P
      RL: BAC (Biological activity or effector, except adverse); BSU (Biological
      study, unclassified); SPN (Synthetic preparation); BIOL (Biological
      study); PREP (Preparation)
          (preparation, 5-HT1A serotonin receptor antagonist and serotonin transporter
          activity, and structure-activity relationship of
          aryl(arylpiperazinyl)propanes)
RN   328248-23-3 CAPLUS
CN   Pyrimidine, 2-[4-[3-phenyl-3-[4-(trifluoromethyl)phenoxy]propyl]-1-
      piperazinyl]- (CA INDEX NAME)
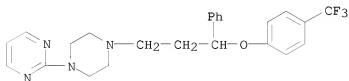
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L2          6 S L1 FULL

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L4              STRUCTURE UPLOADED
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L6          7 S L5 FULL

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FULL ESTIMATED COST                              39.98       426.74

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
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